Aspergillus fumigatus pneumonia in neutropenic patients receiving fuconazole for infection due to candida species: Is amphotericin B combined with fluconazole the appropriate answer?

Pahls, S ; Schaffner, A

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Aspergillus fumigatus Pneumonia in Neutropenic Patients Receiving Fluconazole for Infection Due to *Candida* Species: Is Amphotericin B Combined with Fluconazole the Appropriate Answer?

SIR—Meis et al. [1] rightly remind us in their recent letter that fluconazole is insufficient therapy for invasive aspergillosis; they summarize the cases of four neutropenic patients who died of invasive aspergillosis while receiving fluconazole therapy for invasive candidiasis [1]. However, the conclusion drawn from these observations raises some doubt. The authors justifiably state that fluconazole should not be used as empirical antifungal therapy in patients with suspected pulmonary mycoses, since most mycotic infections are caused by *Aspergillus* species [2–4], and these fungi are relatively resistant to fluconazole [5]. Consequently, Meis and collaborators conclude that clinicians "consider combining amphotericin B with fluconazole ab initio for treating proven candidal infection in any severely immunosuppressed patients, since they are also most at risk from infection with both molds and azole-resistant yeasts."

This recommendation deviates from several recent authoritative recommendations on the use of amphotericin B, with or without flucytosine, as standard therapy for invasive candidiasis and/or aspergillosis [6–12]. Furthermore, the possibility of antagonism between fluconazole (as well as other azoles) and amphotericin B raises concern. Azoles inhibit ergosterol synthesis and thereby eliminate the target for the activity of amphotericin B [13, 14]. This antagonism has been widely confirmed for *Candida* species and aspergilli on the basis of data from in vitro studies [13–16] as well as those from experimental infections [16–19]. Published data on the antifungal activity of fluconazole plus amphotericin B are admittedly scarce, yet it is not surprising that such antagonism can be brought about without difficulty (figure 1). Therefore, in the absence of clinical evidence that fluconazole combined with amphotericin B is superior to monotherapy with amphotericin B or a combination of amphotericin B plus flucytosine, we caution against the widespread use of combined therapy with amphotericin B and fluconazole for candidiasis or aspergillosis.

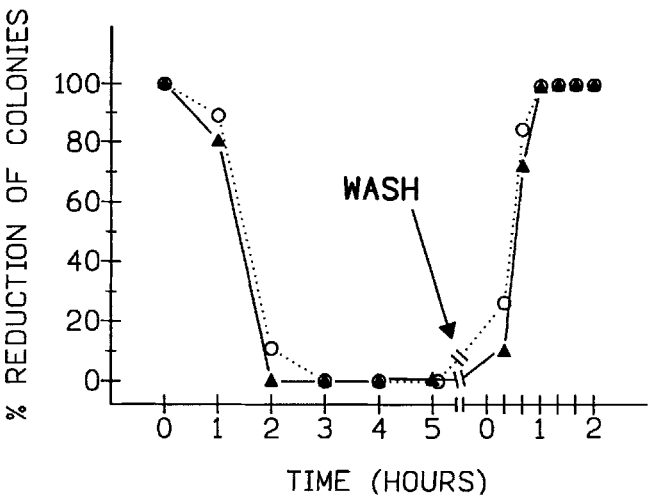

Figure 1. Strain SD-1 of *Candida albicans*, grown overnight in Sabouraud dextrose broth, was exposed at a density of 10^6 cells/mL in minimal essential medium (MEM; Gibco Europe, Basel, Switzerland) to 0.25 mg/L (○) or 0.5 mg/L (▲) of fluconazole. At indicated times (hours 0–5), fungal cells were washed three times in MEM and serial dilutions were transferred to casitone agar plates with or without amphotericin B (2.5 mg/L) for determination of the percentage of yeast cells inhibited by amphotericin B. To maintain the effect of fluconazole during exposure to amphotericin B, all casitone plates were supplemented with a subinhibitory concentration of fluconazole. After 5 hours, <0.1% of the yeast cells remained susceptible to amphotericin B, and exposure to fluconazole was stopped by washing the yeast cells in prewarmed MEM (WASH) prior to further incubation in MEM without antimycotics. While pretreatment with fluconazole for 2 hours was necessary to induce full antagonism between fluconazole and amphotericin B, yeast cells grown in MEM without antifungal agents fully regained their susceptibility to amphotericin B within 1 hour after washing. Reduction in the number of colonies by exposure to amphotericin B is the mean based on results with duplicate tubes from one of two comparable experiments.

Stephan Pahls and Andreas Schaffner
Department of Medicine, Universitätsspital, Zürich, Switzerland

Reprints or correspondence: Dr. Andreas Schaffner, Medizinische Klinik, Universitätsspital Zürich, Ramistrasse 100, Room AA23, CH-8091 Zürich, Switzerland.

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Reply

SIR—We are not alone in our concern about the risk for the development of invasive aspergillosis in patients who are being treated with fluconazole [1]. Kappe and colleagues [2] noted four such cases and concur with our view that the drug should not be given alone to manage persistent fever when the patient is at high risk of developing aspergillosis. Nevertheless, Drs. Pahls and Schaffner are quite correct in highlighting the potential for antagonism between amphotericin B and the azoles, since this antagonism was shown to occur when the lipophilic agent ketoconazole was evaluated in a murine model of invasive aspergillosis [3]. However, the outcome of exposing *Candida albicans* to a combination of the polyene and either miconazole or ketoconazole appears to be critically dependent on the experimental conditions; short-term incubation results in antagonism, whereas the opposite occurs after prolonged exposure [4].

Drs. Pahls and Schaffner report antagonism between amphotericin B and fluconazole (at a dose of 0.25–0.5 mg/L), yet Scheven and Scheven [5] failed to detect any interaction despite prolonged preincubation of yeasts with 10–20 times the amount of drug as that found in human serum following administration of a 400-mg dose. Moreover, there is no evidence to support antagonism between the drugs in patients who have been treated with high doses of fluconazole [6] or in a leukopenic rabbit model of invasive aspergillosis [7]. This does not necessarily mean that Drs. Pahls and Schaffner are dealing with a laboratory curiosity; rather, the application of laboratory findings to the patient and vice versa is never straightforward and must be approached from the widest context possible.

Jacques F. Meis, J. Peter Donnelly, Jacomiena A. Hoogkamp-Korstanje, and Ben E. De Pauw
Department of Medical Microbiology and Hematology, University Hospital Nijmegen, Nijmegen, the Netherlands

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Reprints or correspondence: Dr. Jacques F. Meis, Department of Medical Microbiology, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands.

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